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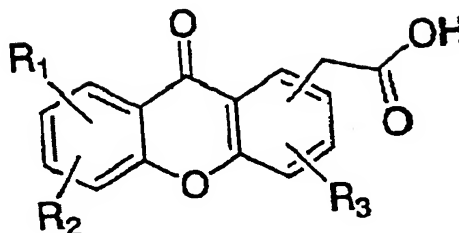
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# EUROPEAN PATENT OFFICE

## Patent Abstracts of Japan

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APPLICANT : OAKLAND UNISERVICES LTD;  
INVENTOR : WILSON WILLIAM R;  
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31:337 )

TITLE : COMBINATION THERAPY FOR  
CANCER



(I)

ABSTRACT : PROBLEM TO BE SOLVED: To provide a method for treating cancer by which the public is at least provided with a useful choice.

SOLUTION: This method comprises a stage of either simultaneously or sequentially administering (i) a compound selected from paclitaxel and docetaxel and (ii) a compound represented by the following formula (wherein R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are each independently selected from the group consisting of H, a 1-6C alkyl, a halogen, CF<sub>3</sub>, CN, NO<sub>2</sub>, NH<sub>2</sub>, OH, OR, NHCOR, NHSO<sub>2</sub>R, SR, SO<sub>2</sub>R and NHR) or a pharmaceutically permissible salt or ester thereof to a mammal in need of the treatment.

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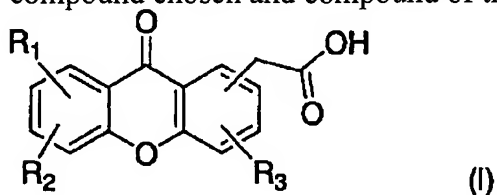
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## CLAIMS

[Claim(s)]

[Claim 1] the mammals which need such treatment in the treatment method of cancer -- simultaneous -- or -- continuous -- (i) paclitaxel (paclitaxel) and DOSETA cheating on the fare (docetaxel) from -- the compound chosen and compound of the (ii) following formula [Formula 1]

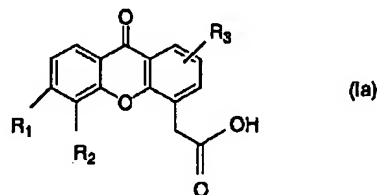


(R1, R2, and R3 among a formula) H and C1 -C6 An alkyl, a halogen, and CF3 CN and NO2 NH2 OH, OR, NHCOR, NHSO2 R, SR, SO2 It is independently chosen out of the group which consists of R and NHR, respectively. Depending on the case, it is C1 by which R was replaced each by one or more substituents as which it is independently chosen out of a hydroxy \*\* amino \*\*\*\*\* methoxy. -C6 It is an alkyl. R1 R2 and R3 Each May exist in any position of the 1-8th place which can be used, and it sets to each of; and the ring formula ring of a formula (I). even two of methine (-CH=) machines replace with an AZA (-N=) machine -- you may have --; and R1 R2 And R3 Any two may be combined together additionally, a -CH=CH-CH=CH-machine may be expressed, and this basis may form a condensation 6 member ring with the carbon or the nitrogen atom which it has combined.

Or a method including the stage of prescribing for the patient the salt or ester which can be permitted pharmacologically.

[Claim 2] The way according to claim 1 the mammals are Homo sapiens.

[Claim 3] The compound of a formula (I) is a compound of the following formula. [Formula 2]



Or the method according to claim 1 or 2 of being the salt or ester which can be permitted pharmacologically.

[Claim 4] The way according to claim 3 the compound of a formula (Ia) is a 5 and 6-dimethyl Korean geisha TENON-4-acetic acid, its salt which can be permitted pharmacologically, or ester.

[Claim 5] Use of the compound of a formula (I) according to claim 1 in manufacture of the medicine which treats mammalian cancer by \*\*\*\*\* (ing) a medicine and the compound chosen from paclitaxel and DOSETA cheating on the fare continuously or simultaneous, its salt which can be permitted pharmacologically, or ester.

[Claim 6] Use of the compound chosen from the DOSETA cheating on the fare and paclitaxel in manufacture of the medicine which treats mammalian cancer by \*\*\*\*\* (ing) a medicine, and the compound, its salt which can be permitted pharmacologically or ester of a formula (I) according to claim 1 continuously or simultaneous.

[Claim 7] The medicine constituent suitable for treating the cancer which contains the compound of a formula (I) according to claim 1, its salt which can be permitted pharmacologically or ester, and the compound chosen from paclitaxel and DOSETA cheating on the fare in combination with one or more the support or the excipients which can be permitted pharmacologically.

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[Translation done.]

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## DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Industrial Application] this invention relates to the method of treating cancer.

[0002]

[Description of the Prior Art] It is known that a compound 5 and a 6-dimethyl Korean geisha TENON-4-acetic acid (DMXAA) have remarkable antitumor activity to Homo sapiens's tumor by which the xenograft was carried out to the tumor of a mouse and the immune disorder mouse. It has been proved by research that it is mainly as a result of prevention of a blood flow even if this activity is not perfect alternatively inside a tumor. However, DMXAA does not show clinically most proof of the anticancer activity which can be performed in Homo sapiens till today.

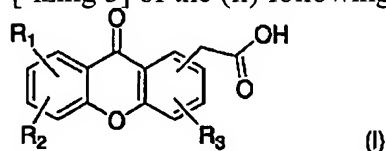
[0003] These people to a thing surprising now The compound of Korean geisha TENON acetic acids (DMXAA is one of them), By prescribing that it is simultaneous or continuously both paclitaxel or DOSETA cheating on the fare (compound of both taxane (taxane) of an anticancer agent) for the patient the anticancer effect of the combination -- one of \*\* -- it attaches independently, a twist is also far large, and it is a header about the increase in antitumor activity which exceeds the sum total of the effect of each \*\* greatly taking place -- it carried out

[0004]

[Problem(s) to be Solved by the Invention] It was the purpose of this invention to offer the treatment method of cancer of providing the public with useful option at least, in consideration of this background.

[0005]

[Means for Solving the Problem] therefore, the mammals for which this invention needs such treatment in the treatment method of cancer in the 1st page -- simultaneous -- or -- continuous -- (i) paclitaxel (paclitaxel) and DOSETA cheating on the fare (docetaxel) from -- the compound chosen and compound [-izing 3] of the (ii) following formula



[0006] (R1, R2, and R3 among a formula) H and C1 -C6 An alkyl, a halogen, and CF3 CN and NO2 NH2 OH, OR, NHCOR, NHSO2 R, SR, SO2 It is independently chosen out of the group which consists of R and NHR, respectively. Depending on the case, it is C1 by which R was replaced each by one or more substituents as which it is independently chosen out of a hydroxy \*\* amino \*\*\*\*\* methoxy. -C6 It is an alkyl. R1 R2 and R3 Each May exist in any position of the 1-8th place which can be used, and it sets to each of; and the ring formula ring of a formula (I). even two of methine (-CH=) machines replace with an AZA (-N=) machine -- you may have --; and R1 R2 And R3 Any two may be combined together additionally, a -CH=CH-CH=CH-machine may be expressed, and this basis may form a condensation 6

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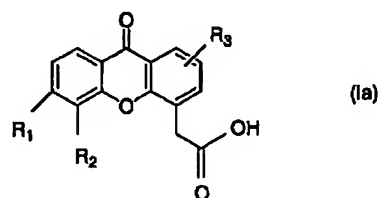
Or a method including the stage of prescribing for the patient the salt or ester which can be permitted pharmacologically is offered.

[0007] Preferably, the mammals are Homo sapiens.

[0008] Preferably, the compound of a formula (I) is a compound of the following formula.

[0009]

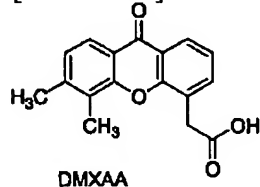
[Formula 4]



[0010] The compound of a formula (I) is a 5 which has following formula, and 6-dimethyl Korean geisha TENON-4-acetic acid most preferably.

[0011]

[Formula 5]



[0012] It is \*\*\*\*\* (co-administration) continuously or simultaneous about the compound with which this invention is chosen from a medicine, and paclitaxel and DOSETA cheating on the fare in other fields. Use of the compound of the formula (I) defined above in manufacture of the medicine which treats mammalian cancer, its salt which can be permitted pharmacologically, or ester is offered by carrying out.

[0013] Furthermore, in other fields, this invention offers use of the compound chosen from the DOSETA cheating on the fare and paclitaxel in manufacture of the medicine which treats mammalian cancer by \*\*\*\*\* (ing) a medicine, and the compound, its salt which can be permitted pharmacologically or ester of the formula (I) defined above continuously or simultaneous.

[0014] Furthermore, in other fields, this invention is combination with one or more the support or the excipients which can be permitted pharmacologically, and offers the medicine constituent suitable for treating the cancer containing the compound of the formula (I) defined above, its salt which can be permitted pharmacologically or ester, and the compound chosen from paclitaxel and DOSETA cheating on the fare.

[0015] Although this invention is as having given the definition above generally, the following description also includes the embodiment which offers an example. These concrete embodiments are described with an accompanying drawing.

[0016] C3 of a female which prescribed DMXAA, paclitaxel, DMXAA, and paclitaxel for the patient as follows so that drawing 1 might be stated to an example 1 detailed in the letter : which shows each typical tumor growth curve about a H/HeN mouse -- A: -- control, B:DMXAA (80micro mol/(kg)), C:paclitaxel (42.1micro mol/(kg)), and D:DMXAA(80micro mol/(kg))+ paclitaxel (31.6micro mol/(kg))

[0017] As the definition was given above, this invention relates to the method of treating cancer.

[0018] this invention exists in the knowledge of the very big multiplication-interaction between the compound of the Korean geisha TENON acetic acids which have the formula (I) which these people did not expect above and was defined, and two compounds (paclitaxel and DOSETA cheating on the fare)

of the taxane of an anticancer agent. To a host (it is determined by loss-weight and mortality rate like) animal, especially simultaneous medication of both the compound 5 of a formula (I), a 6-dimethyl Korean geisha TENON-4-acetic acid (DMXAA), and paclitaxel or DOSETA cheating on the fare shows toxicity also with one of high \*\* independent twists, and needs a moderate reduction of the dosage of one or other \*\* in the combination. However, this host toxicity interaction is a low farther than the increase in antitumor activity. consequently, the anticancer effect attained -- one of \*\* -- it attaches independently, and a twist is also dramatically large and exceeds the sum total of the effect of each \*\* greatly Therefore, it is expected that the combination of a 5 and 6-dimethyl Korean geisha TENON-4-acetic acid or other compounds of a formula (I), and taxane anticancer medicine paclitaxel and DOSETA cheating on the fare has clinical usefulness in the treatment of cancer.

[0019] Therefore, the treatment method of this invention includes the stage of medicating a patient with paclitaxel or DOSETA cheating on the fare, and the compound, its salt which can be permitted pharmacologically or ester of the formula (I) defined above it being simultaneous or continuously.

[0020] The compound of a formula (I) is known and can be prepared using a known method to this contractor. For example, the compounds and those processes of a formula (I) are :Journal of Medicinal Chemistry 34 (1) indicated by the following bibliography. : 217 to 22 months, January, 1991; Journal of Medicinal Chemistry 34 (2): 491 February, 1991 [ -6 or ]; Journal of Medicinal Chemistry 33 (5): 1375 to 9 months, May, 1990; Journal of Medicinal Chemistry 34 (9): 2864 September, 1991 [ -70 or ]; and Journal of Medicinal Chemistry 32 (4): The content is incorporated into the specification in 793 April, 1989 [ -9 or ] for reference.

[0021] Taxane paclitaxel (taxol (taxol)) and DOSETA cheating on the fare (Taxotere (taxotere)) are also well-known compounds, and can be similarly prepared by the known method to this contractor.

[0022] Generally the compound of a formula (Ia) and (substituent R1 and R2 being in the 5th place and the 6th place among a formula) among the compounds of the formula (I) defined above is desirable to the use in the method of this invention. Especially a desirable compound is a 5 and 6-dimethyl Korean geisha TENON-4-acetic acid. The process of this compound is Journal of Medicinal Chemistry 34 (1). : It is indicated in 217 to 22 months, and January, 1991.

[0023] You may medicate a patient with the compound of a formula (I), paclitaxel, or DOSETA cheating on the fare by all the suitable pharmaceutical forms. For example, you may administer a compound intravenously to this contractor conveniently using a known tablet about each compound.

[0024] You may prescribe that it is simultaneous or continuously the compound of a formula (I), paclitaxel, or DOSETA cheating on the fare for the patient. namely, prescribing the compound of a formula (I) for the patient for taxane -- simultaneously, before prescribing a medicine for the patient, you may prescribe a medicine for the patient behind

[0025] However, generally it is desirable to prescribe paclitaxel or DOSETA cheating on the fare for the patient first, and to prescribe the compound of a formula (I) for the patient preferably subsequently to [ within about 2 - 4 hours ] as early as possible.

[0026] this invention is stated more to a detail with reference to the following un-limiting-example.

[0027]

[Embodiments of the Invention] C3 of the female from the stock stored into liquid nitrogen in the 6th transplant generation in breast cancer MDAH-MCa-4 tumor of example 1 mouse The H/HeN mouse was made to grow, and it cultivated and was used for the experiment in an octavus transplant generation. The tumor for an experiment was grown by carrying out the muscular inscribed kind of the cell suspension (cell made into the 5mg tray pack) of 20microl to right gastrocnemius. Random sampling of the animal was carried out to the treatment group, and after about 18 days of inoculation, when the diameter of the foot which has a tumor amounted to 10-11mm (tumor which is about 0.6g), it treated with the medicine. (DMXAA) Or the medicine was prescribed only once for the patient by the intraperitoneal injection which uses the volume of 0.01 ml/g weight about each compound in a claim forehead's (chremphor) phosphoric-acid buffer salting-in liquid gestalt (paclitaxel). Both compounds were essentially simultaneously prescribed for the patient (to less than 1 minute). The determination of a case fatality rate

and measurement of the weight four - five days after medicine treatment estimated host toxicity. The diameter of the foot which has a tumor was measured 3 times per week until the value exceeded 13mm (tumor which is about 1.4g). The animal was then dead. The growth curve about each tumor was shown like drawing 1 , and it decided on the time (TTE, time from treatment to a terminal point) to a terminal point about each mouse. TTE of middle and an average was determined about each treatment group. Tumor-growth delay of the average about each group was calculated as a difference of TTE of the average about a treatment group, and TTE of the average about a control group. The statistical significance of the anti-tumor effect is examined using ANOVA, and, subsequently it is DANNETTO (Dunnett). It examined and p value about the significance of the difference between each groups was determined.

[0028] The data of drawing 1 and Table 1 show that reduction of the dosage from 42micro mol (it is not toxicity clearly about a paclitaxel independent)/kg to 31.6micro mol/kg is needed, when a toxic clear increase is seen in combination and paclitaxel is combined with DMXAA. When the latter dosage was combined with DMXAA (80micro mol/(kg)), it survived without the bigger loss weight than the time of a DMXAA independent by the health condition excellent in all the mice. if paclitaxel is independent -- this model -- setting -- antitumor activity -- almost -- not having been generated (it being the growth retardation on the 4th at kg in 42micro mol /) -- it combined and came out and activity increased dramatically The combination with DMXAA of 31.6micro mol [ /kg ] taxol produced three sevenths of healing with the growth retardation of the average on the 50th (it will be longer for 42 days than the time of a DMXAA independent) about four tumors which recurred. Big growth retardation was also seen with 17.8micro mol [ / ] one healing by kg in combination with DMXAA in the dosage level of two examined lower taxol (Table 1).

[0029] Table 1: Paclitaxel, and independent and activity to MDAH-MCa-4 tumor which combines and comes out of DMXAA. Experiment conditions were as above-mentioned.

[0030]

[Table 1]

パクリタキセル 用量 ( $\mu\text{mol}/\text{kg}$ )	DMXAA 用量 ( $\mu\text{mol}/\text{kg}$ )	実験/ 群コード	マウスの数			%体重変化 (4~5日)		成長遅延 (日) *				DMXAAのみに追加 された成長遅延 (日) *			
			治療	死亡	治癒	平均	SEM	平均	SEM	p (コントロール ルに対して)	平均	SEM	p (DMXAA 単独に対して)		
0	0	113/A	7	0	0	2.1	1.3	0	0.9						
23.7	0	113/C	7	0	0	0.4	1.3	0	1.1	1					
31.6	0	113/D	7	0	0	1.9	0.8	0.1	1.7	1					
42.1	0	113/E	7	0	0	0.3	1.1	4.3	1.5	0.12					
0	80	113/B	7	0	0	-4.1	1.3	8.3	2.3	0.0002					
17.8	80	113/Z	7	0	1	-3.8	1.3	41.7	10.0		33.4	10.3	0.046		
23.7	80	113/F	7	1	0	-6.7	0.7	37.6	12.7		29.3	12.9	0.11		
31.6	80	113/G	7	0	3	-3.9	1.2	50.5	12.8		42.2	13.0	0.0001		
42.1	80	113/H	3	3	0										

h

g

cg b

eb cg e e

[0031] Except the mouse which recovered from this analysis.

[0032] The effect of changing the time of medication of DMXAA to paclitaxel was examined using the same experiment method as example 2 example 1. This experiment is among a present progressive and only temporary analysis has received it (a tumor is based at the middle time which reaches terminal point size). This temporary analysis (Table 2) corroborates the big interaction proved in the example 1. At this time, the grade of the reaction to the group which treated or carried out simultaneous medication of this by DMXAA 4 hours 1 hour 1 hour before paclitaxel, after paclitaxel, or after paclitaxel is not discriminable. A reaction is not large about DMXAA prescribed for the patient 4 hours before paclitaxel. This result proves a latus time zone rationally for an interaction.

[0033] Table 2: Paclitaxel, and independent and activity to MDAH-MCa-4 tumor in timing from which medication of two medicines which combine and come out differs of DMXAA. Experiment conditions were as above-mentioned. This is temporary analysis (an animal is still under observation). About the group which shows a big reaction, many have the tumor smaller than terminal point size from the half of an animal, and the median is not determined yet.

[0034]

[Table 2]

パクリタキセル 用量	DMXAA 用量	タイミング	実験/ 群コード	マウスの数		%体重変化 (4~5日)		成長遅延 (日)
				治療	死亡	平均	SEM	
( $\mu\text{mol/kg}$ )	( $\mu\text{mol/kg}$ )							メジアン
0	0		120/A	6	1	-1.2	1.6	0
0	80		120/B	7	2	-6.0	2.7	17.9
23.7	0		120/C	7	1	-0.1	4.2	3.5
23.7	80	パクリタキセルの 4時間後にDMXAA	120/D	12	4	-7.4	2.4	>31
23.7	80	パクリタキセルの 1時間後にDMXAA	120/E	12	2	-5.8	3.6	>41
23.7	80	共に	120/F	12	2	-8.6	2.2	>31
23.7	80	パクリタキセルの 1時間前にDMXAA	120/G	12	0	-10.1	1.1	>32
23.7	80	パクリタキセルの 4時間前にDMXAA	120/H	12	2	-9.0	1.6	31

[0035] Using the same experiment method as an example 1, combining both compounds, simultaneous medication of the interaction with DMXAA of example 3 DOSETA cheating on the fare was carried out, and it was examined. This experiment is among a present progressive and only temporary analysis has received it (a tumor is based at the middle time which reaches terminal point size). this temporary analysis (Table 3) -- DOSETA cheating on the fare -- if independent, although the activity to MDAH-MCa-4 tumor is essentially lacked -- the combination of DOSETA cheating on the fare and DMXAA -- DMXAA -- the independent thing farther been activity is shown Thus, it is far high rather than the activity of combination is expected about paclitaxel based on the activity of independent \*\*.

[0036] Table 3: DOSETA cheating on the fare, and independent and activity to MDAH-MCa-4 tumor to combine (simultaneous medication was carried out) of DMXAA. Experiment conditions were as above-mentioned. This is temporary analysis (an animal is still under observation). About the group which shows a big reaction, many have the tumor smaller than terminal point size from the half of an animal, and the median is not determined yet.

[0037]

[Table 3]

ドセタキセル 用量	DMXAA 用量	実験/ 群コード	マウスの数		%体重変化 (4~5日)		成長遅延 (日)
( $\mu\text{mol/kg}$ )	( $\mu\text{mol/kg}$ )		治療	死亡	平均	SEM	メジアン
0	0	120/J	7	1	0.58	0.74	0
0	80	120/K	7	0	-4.8	1.3	10.5
17.8	0	120/L	2	0	-1.8	1.2	-1.7
23.7	0	120/M	5	0	-4.1	1.3	0.8
13.3	80	120/N	8	0	-6.8	1.5	18
17.8	80	120/P	8	0	-7.2	1.2	>21
23.7	80	120/Q	8	0	-7.4	1.2	26

[0038] this invention offers how to have improved the cancer treatment that finding out far-reaching clinical usefulness is expected so that clearly from the above-mentioned description and an example.

[0039] A specific description provided with this contractor about it is a mere typical example, and he will understand that this invention is not limited to it.

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TECHNICAL FIELD

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[Industrial Application] this invention relates to the method of treating cancer.

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PRIOR ART

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[Description of the Prior Art] It is known that a compound 5 and a 6-dimethyl Korean geisha TENON-4-acetic acid (DMXAA) have remarkable antitumor activity to a man's neoplasm by which the xenograft was carried out to the neoplasm of a mouse and the immune disorder mouse. It has been proved by research that it is mainly as a result of prevention of a blood flow even if this activity is not perfect alternatively inside a neoplasm. However, DMXAA does not show clinically most proof of the anticancer activity which can be performed in the man till today.

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TECHNICAL PROBLEM

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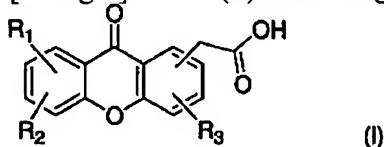
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## MEANS

[Means for Solving the Problem] therefore, the mammals for which this invention needs such treatment in the treatment method of cancer in the 1st page -- simultaneous -- or -- continuous -- (i) paclitaxel (paclitaxel) and DOSETA cheating on the fare (docetaxel) from -- the compound chosen and compound [izing 3] of the (ii) following formula



[0006] (R1, R2, and R3 among a formula) H and C1 -C6 An alkyl, a halogen, and CF3 CN and NO2 NH2 OH, OR, NHCOR, NHSO2 R, SR, SO2 It is independently chosen out of the group which consists of R and NHR, respectively. Depending on the case, it is C1 by which R was replaced each by one or more substituents as which it is independently chosen out of a hydroxy \*\* amino \*\*\*\*\* methoxy. -C6 It is an alkyl. R1 R2 and R3 Each May exist in any position of the 1-8th place which can be used, and it sets to each of; and the ring formula ring of a formula (I). even two of methine (-CH=) machines replace with an AZA (-N=) machine -- you may have --; and R1 R2 And R3 Any two may be combined together additionally, a -CH=CH-CH=CH-machine may be expressed, and this basis may form a condensation 6 member ring with the carbon or the nitrogen atom which it has combined.

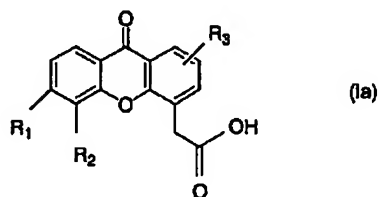
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[0009]

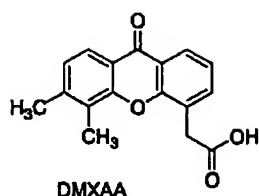
[Formula 4]



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[Formula 5]



[0012] It is \*\*\*\*\* (co-administration) continuously or simultaneous about the compound with which this invention is chosen from a medicine, and paclitaxel and DOSETA cheating on the fare in other fields. Use of the compound of the formula (I) defined above in manufacture of the medicine which treats mammalian cancer, its salt which can be permitted pharmacologically, or ester is offered by carrying out.

[0013] Furthermore, in other fields, this invention offers use of the compound chosen from the DOSETA cheating on the fare and paclitaxel in manufacture of the medicine which treats mammalian cancer by \*\*\*\*\* (ing) a medicine, and the compound, its salt which can be permitted pharmacologically or ester of the formula (I) defined above continuously or simultaneous.

[0014] Furthermore, in other fields, this invention is combination with one or more the support or the excipients which can be permitted pharmacologically, and offers the medicine constituent suitable for treating the cancer containing the compound of the formula (I) defined above, its salt which can be permitted pharmacologically or ester, and the compound chosen from paclitaxel and DOSETA cheating on the fare.

[0015] Although this invention is as having given the definition above generally, the following description also includes the embodiment which offers an example. These concrete embodiments are described with an accompanying drawing.

[0016] C3 of a female which prescribed DMXAA, paclitaxel, DMXAA, and paclitaxel for the patient as follows so that drawing 1 might be stated to an example 1 detailed in the letter : which shows each typical tumor growth curve about a H/HeN mouse -- A: -- control, B:DMXAA (80micro mol/(kg)), C:paclitaxel (42.1micro mol/(kg)), and D:DMXAA(80micro mol/(kg))+ paclitaxel (31.6micro mol/(kg))

[0017] As the definition was given above, this invention relates to the method of treating cancer.

[0018] this invention exists in the knowledge of the very big multiplication-interaction between the compound of the Korean geisha TENON acetic acids which have the formula (I) which these people did not expect above and was defined, and two compounds (paclitaxel and DOSETA cheating on the fare) of the taxane of an anticancer agent. To a host (it is determined by loss-weight and mortality rate like) animal, especially simultaneous medication of both the compound 5 of a formula (I), a 6-dimethyl Korean geisha TENON-4-acetic acid (DMXAA), and paclitaxel or DOSETA cheating on the fare shows toxicity also with one of high \*\* independent twists, and needs a moderate reduction of the dosage of one or other \*\* in the combination. However, this host toxicity interaction is a low farther than the increase in antitumor activity. consequently, the anticancer effect attained -- one of \*\* -- it attaches independently, and a twist is also dramatically large and exceeds the sum total of the effect of each \*\* greatly Therefore, it is expected that the combination of a 5 and 6-dimethyl Korean geisha TENON-4-acetic acid or other compounds of a formula (I), and taxane anticancer medicine paclitaxel and DOSETA cheating on the fare has clinical usefulness in the treatment of cancer.

[0019] Therefore, the treatment method of this invention includes the stage of medicating a patient with paclitaxel or DOSETA cheating on the fare, and the compound, its salt which can be permitted pharmacologically or ester of the formula (I) defined above it being simultaneous or continuously.

[0020] The compound of a formula (I) is known and can be prepared using a known method to this contractor. For example, the compounds and those processes of a formula (I) are :Journal of Medicinal Chemistry 34 (1) indicated by the following bibliography. : 217 to 22 months, January, 1991; Journal of Medicinal Chemistry 34 (2): 491 February, 1991 [ -6 or ]; Journal of Medicinal Chemistry 33 (5): 1375 to 9 months, May, 1990;

Journal of Medicinal Chemistry 34 (9): 2864 September, 1991 [ -70 or ]; and Journal of Medicinal Chemistry 32 (4): The content is incorporated into the specification in 793 April, 1989 [ -9 or ] for reference.

[0021] Taxane paclitaxel (taxol (taxol)) and DOSETA cheating on the fare (Taxotere (taxotere)) are also well-known compounds, and can be similarly prepared by the known method to this contractor.

[0022] Generally the compound of a formula (Ia) and (substituent R1 and R2 being in the 5th place and the 6th place among a formula) among the compounds of the formula (I) defined above is desirable to the use in the method of this invention. Especially a desirable compound is a 5 and 6-dimethyl Korean geisha TENON-4-acetic acid. The process of this compound is Journal of Medicinal Chemistry 34 (1). : It is indicated in 217 to 22 months, and January, 1991.

[0023] You may medicate a patient with the compound of a formula (I), paclitaxel, or DOSETA cheating on the fare by all the suitable pharmaceutical forms. For example, you may administer a compound intravenously to this contractor conveniently using a known tablet about each compound.

[0024] You may prescribe that it is simultaneous or continuously the compound of a formula (I), paclitaxel, or DOSETA cheating on the fare for the patient. namely, prescribing the compound of a formula (I) for the patient for taxane -- simultaneously, before prescribing a medicine for the patient, you may prescribe a medicine for the patient behind

[0025] However, generally it is desirable to prescribe paclitaxel or DOSETA cheating on the fare for the patient first, and to prescribe the compound of a formula (I) for the patient preferably subsequently to [ within about 2 - 4 hours ] as early as possible.

[0026] this invention is stated more to a detail with reference to the following un-limiting-example.

[0027]

[Embodiments of the Invention] C3 of the female from the stock stored into liquid nitrogen in the 6th transplant generation in breast cancer MDAH-MCa-4 tumor of example 1 mouse The H/HeN mouse was made to grow, and it cultivated and was used for the experiment in an octavus transplant generation. The tumor for an experiment was grown by carrying out the muscular inscribed kind of the cell suspension (cell made into the 5mg tray pack) of 20microl to right gastrocnemius. Random sampling of the animal was carried out to the treatment group, and after about 18 days of inoculation, when the diameter of the foot which has a tumor amounted to 10-11mm (tumor which is about 0.6g), it treated with the medicine. (DMXAA) Or the medicine was prescribed only once for the patient by the intraperitoneal injection which uses the volume of 0.01 ml/g weight about each compound in a claim forehead's (chremphor) phosphoric-acid buffer salting-in liquid gestalt (paclitaxel). Both compounds were essentially simultaneously prescribed for the patient (to less than 1 minute). The determination of a case fatality rate and measurement of the weight four - five days after medicine treatment estimated host toxicity. The diameter of the foot which has a tumor was measured 3 times per week until the value exceeded 13mm (tumor which is about 1.4g). The animal was then dead. The growth curve about each tumor was shown like drawing 1 , and it decided on the time (TTE, time from treatment to a terminal point) to a terminal point about each mouse. TTE of middle and an average was determined about each treatment group. Tumor-growth delay of the average about each group was calculated as a difference of TTE of the average about a treatment group, and TTE of the average about a control group. The statistical significance of the anti-tumor effect is examined using ANOVA, and, subsequently it is DANNETTO (Dunnett). It examined and p value about the significance of the difference between each groups was determined.

[0028] The data of drawing 1 and Table 1 show that reduction of the dosage from 42micro mol (it is not toxicity clearly about a paclitaxel independent)/kg to 31.6micro mol/kg is needed, when a toxic clear increase is seen in combination and paclitaxel is combined with DMXAA. When the latter dosage was combined with DMXAA (80micro mol/(kg)), it survived without the bigger loss weight than the time of a DMXAA independent by the health condition excellent in all the mice. if paclitaxel is independent -- this model -- setting -- antitumor activity -- almost -- not having been generated (it being the growth retardation on the 4th at kg in 42micro mol /) -- it combined and came out and activity increased dramatically The combination with DMXAA of 31.6micro mol [ /kg ] taxol produced three sevenths of

healing with the growth retardation of the average on the 50th (it will be longer for 42 days than the time of a DMXAA independent) about four tumors which recurred. Big growth retardation was also seen with 17.8micro mol [ /] one healing by kg in combination with DMXAA in the dosage level of two examined lower taxol (Table 1).

[0029] Table 1: Paclitaxel, and independent and activity to MDAH-MCa-4 tumor which combines and comes out of DMXAA. Experiment conditions were as above-mentioned.

[0030]

[Table 1]

バクリタキセル 用量 ( $\mu\text{mol/kg}$ )	DMXAA 用量 ( $\mu\text{mol/kg}$ )	実験/ 群コード	マウスの数			%体重変化 (4~5日)		成長遅延 (日) *				DMXAAのみに追加 された成長遅延 (日) *			
			治療	死亡	治癒	平均	SEM	平均	SEM	p (コントロール ルに対して)	平均	SEM	p (DMXAA 単独に対して)	平均	SEM
0	0	113/A	7	0	0	2.1	1.3	0	0.9						
23.7	0	113/C	7	0	0	0.4	1.3	0	1.1	1					
31.6	0	113/D	7	0	0	1.9	0.8	0.1	1.7	1					
42.1	0	113/E	7	0	0	0.3	1.1	4.3	1.5	0.12					
0	80	113/B	7	0	0	-4.1	1.3	8.3	2.3	0.0002					
17.8	80	113/Z	7	0	1	-3.8	1.3	41.7	10.0		33.4	10.3	0.046		
23.7	80	113/F	7	1	0	-6.7	0.7	37.6	12.7		29.3	12.9	0.11		
31.6	80	113/G	7	0	3	-3.9	1.2	50.5	12.8		42.2	13.0	0.0001		
42.1	80	113/H	3	3	0										

h

g

cg b

eb cg e e

[0031] Except the mouse which recovered from this analysis.

[0032] The effect of changing the time of medication of DMXAA to paclitaxel was examined using the same experiment method as example 2 example 1. This experiment is among a present progressive and only temporary analysis has received it (a tumor is based at the middle time which reaches terminal point size). This temporary analysis (Table 2) corroborates the big interaction proved in the example 1. At this time, the grade of the reaction to the group which treated or carried out simultaneous medication of this by DMXAA 4 hours 1 hour 1 hour before paclitaxel, after paclitaxel, or after paclitaxel is not discriminable. A reaction is not large about DMXAA prescribed for the patient 4 hours before paclitaxel. This result proves a latus time zone rationally for an interaction.

[0033] Table 2: Paclitaxel, and independent and activity to MDAH-MCa-4 tumor in timing from which medication of two medicines which combine and come out differs of DMXAA. Experiment conditions were as above-mentioned. This is temporary analysis (an animal is still under observation). About the group which shows a big reaction, many have the tumor smaller than terminal point size from the half of an animal, and the median is not determined yet.

[0034]

[Table 2]

パクリタキセル 用量	DMXAA 用量	タイミング	実験/ 群コード	マウスの数		%体重変化 (4~5日)		成長遅延 (日)
( $\mu\text{mol/kg}$ )	( $\mu\text{mol/kg}$ )			治療	死亡	平均	SEM	メジアン
0	0		120/A	6	1	-1.2	1.6	0
0	80		120/B	7	2	-6.0	2.7	17.9
23.7	0		120/C	7	1	-0.1	4.2	3.5
23.7	80	パクリタキセルの 4時間後にDMXAA	120/D	12	4	-7.4	2.4	>31
23.7	80	パクリタキセルの 1時間後にDMXAA	120/E	12	2	-5.8	3.6	>41
23.7	80	共に	120/F	12	2	-8.6	2.2	>31
23.7	80	パクリタキセルの 1時間前にDMXAA	120/G	12	0	-10.1	1.1	>32
23.7	80	パクリタキセルの 4時間前にDMXAA	120/H	12	2	-9.0	1.6	31

[0035] Using the same experiment method as an example 1, combining both compounds, simultaneous medication of the interaction with DMXAA of example 3 DOSETA cheating on the fare was carried out, and it was examined. This experiment is among a present progressive and only temporary analysis has received it (a tumor is based at the middle time which reaches terminal point size). this temporary analysis (Table 3) -- DOSETA cheating on the fare -- if independent, although the activity to MDAH-MCa-4 tumor is essentially lacked -- the combination of DOSETA cheating on the fare and DMXAA -- DMXAA -- the independent thing farther been activity is shown Thus, it is far high rather than the activity of combination is expected about paclitaxel based on the activity of independent \*\*.

[0036] Table 3: DOSETA cheating on the fare, and independent and activity to MDAH-MCa-4 tumor to combine (simultaneous medication was carried out) of DMXAA. Experiment conditions were as above-mentioned. This is temporary analysis (an animal is still under observation). About the group which shows a big reaction, many have the tumor smaller than terminal point size from the half of an animal, and the median is not determined yet.

[0037]

[Table 3]

ドセタキセル 用量	DMXAA 用量	実験/ 群コード	マウスの数		%体重変化 (4～5日)		成長遅延 (日)
( $\mu\text{mol}/\text{kg}$ )	( $\mu\text{mol}/\text{kg}$ )		治療	死亡	平均	SEM	メジアン
0	0	120/J	7	1	0.58	0.74	0
0	80	120/K	7	0	-4.8	1.3	10.5
17.8	0	120/L	2	0	-1.8	1.2	-1.7
23.7	0	120/M	5	0	-4.1	1.3	0.8
13.3	80	120/N	8	0	-6.8	1.5	18
17.8	80	120/P	8	0	-7.2	1.2	>21
23.7	80	120/Q	8	0	-7.4	1.2	26

[0038] this invention offers how to have improved the cancer treatment that finding out far-reaching clinical usefulness is expected so that clearly from the above-mentioned description and an example.

[0039] A specific description provided with this contractor about it is a mere typical example, and he will understand that this invention is not limited to it.

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[Translation done.]

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DESCRIPTION OF DRAWINGS

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[Brief Description of the Drawings]

[Drawing 1] Drawing 1 A -- C3 of the female of control It is the graph which shows the tumor growth curve of a H/HeN mouse.

C3 of a female which prescribed drawing 1 B--DMXAA for the patient It is the graph which shows the tumor growth curve of a H/HeN mouse.

Drawing 1 C -- C3 of a female which prescribed paclitaxel for the patient It is the graph which shows the tumor growth curve of a H/HeN mouse.

C3 of a female which prescribed drawing 1 D--DMXAA and paclitaxel for the patient It is the graph which shows the tumor growth curve of a H/HeN mouse.

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[Translation done.]

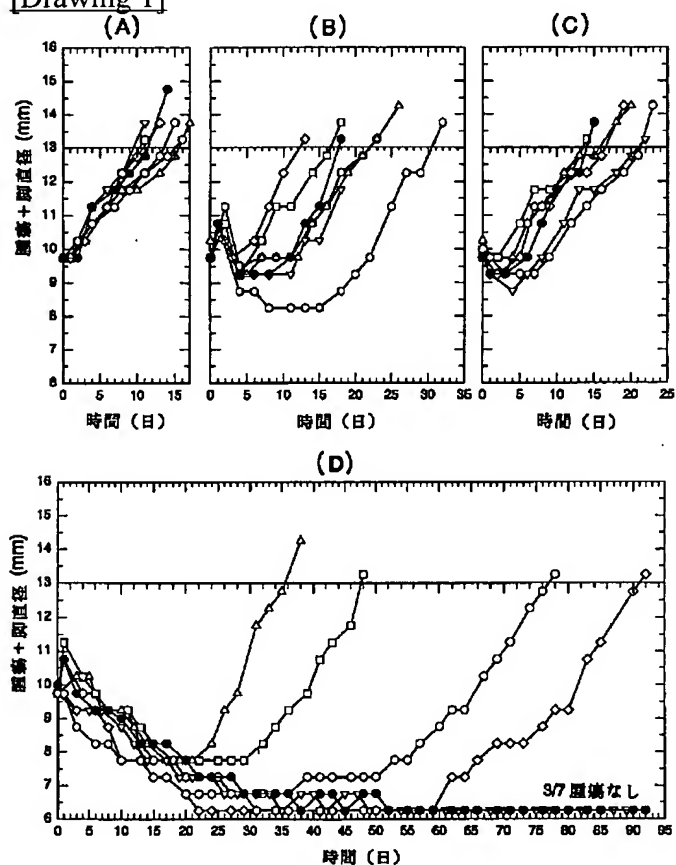
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## DRAWINGS

[Drawing 1]



[Translation done.]